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Distinctive Menkes Disease Variant With Occipital Horns: Delineation of Natural History and Clinical Phenotype

Virginia K. Proud, Holly G. Mussell, Stephen G. Kaler, Daniel W. Young, and Alan K. Percy

Laboratory of Medical Genetics (V.K.P.), Division of Neurology, Department of Pediatrics, University of Alabama School of Medicine (H.G.M., A.K.P.), Birmingham; Department of Pediatric Imaging, Children's Hospital of Alabama, Birmingham, Alabama (D.W.Y.); Clinical Neuroscience Branch, NINDS, NIH, Bethesda, Maryland (S.G.K.); and Departments of Medical Genetics and Pediatrics, Children's National Medical Center and George Washington University, Washington, DC (S.G.K.)

To delineate further the clinical spectrum of Menkes disease, an X-linked recessive disorder of copper transport, we studied 4 related males, ranging in age from 4–38 years, with a unique phenotype that combines manifestations of classical and mild Menkes disease and occipital horn syndrome (OHS). The propositus, an 18-year-old man, was evaluated following an intracerebral hemorrhage at age 15 years and was noted to have marked hypotonia, motor delay with mental retardation, bladder diverticula, failure to thrive, and diarrhea from infancy; seizures from age 3 years; and abnormal hair (pili torti) and face, cutis laxa, and multiple joint dislocations. Radiographic abnormalities included occipital exostoses, tortuous cerebral blood vessels with multiple branch occlusions, and hammer-shaped clavicles. Biochemical studies demonstrated reduced copper and ceruloplasmin levels in serum, and abnormal plasma catecholamine ratios. We reported previously the molecular defect in this family, a splice-site mutation that predicts formation of approximately 20% of the normal Menkes gene product [Kaler et al., 1994: Nat Genet 18:195–202]. Here, we detail the clinical course and physical features and radiographic findings in these 4 individuals, and compare their phenotype with classical and mild Menkes and OHS. Unusual Menkes disease variants such as this may escape recognition due to anomalies that appear inconsistent with the diagnosis, particularly prolonged survival and later onset of seizures. Males with mental retardation and connective tissue abnormalities should be evaluated for biochemical evidence of defective copper transport. © 1996 Wiley-Liss, Inc.

KEY WORDS: Menkes disease, occipital horn syndrome, copper transport, cutis laxa, pili torti, dopamine-β-hydroxylase, plasma catechol levels

INTRODUCTION

Menkes disease is a rare X-linked recessive disorder of copper transport with incidence estimates ranging from 1 in 100,000–250,000 births [Menkes et al., 1962; Danks et al., 1972; Tønnesen et al., 1991; Kaler, 1994]. Key features characteristics of the classic phenotype are summarized in Table I. Survival beyond early childhood is unusual [Baerlocher and Nadal, 1988]. Magnetic resonance imaging (MRI) of the brain demonstrates dysmyelination, cerebral and cerebellar atrophy, ventriculomegaly, and subdural fluid collections. Tortuosity of cerebral blood vessels is evident with magnetic resonance angiography (MRA) [Johnsen et al., 1991; Jacobs et al., 1993; Takahashi et al., 1993]. Wormian skull bones, metaphyseal spurring of long bones, and anterior flaring and fracture of ribs are evident on plain radiographs [Stanley et al., 1976]. The phenotype is related to deficient activity of copper-dependent enzymes. Biochemical findings include decreased serum copper and ceruloplasmin levels [Danks et al., 1972] and characteristic plasma and cerebrospinal fluid neurochemical profiles [Kaler et al., 1993], reflecting partial deficiency of dopamine-β-hydroxylase (DBH), a copper-dependent enzyme. The Menkes disease gene encodes a putative copper-transporting ATPase [Vulpe et al., 1993; Chelly et al., 1993; Mercer et al., 1993].

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Address reprint requests to Holly G. Mussell, M.D., 516 Ambulatory Care Center, Children's Hospital of Alabama, 1600 7th Ave. South, Birmingham, AL 35233.

TABLE I. Comparison of Clinical Findings in Study Patients to Established Menkes Phenotypes*

	Patient 1	Patient 2	Patient 3	Patient 4	Classical Menkes[a]	Mild Menkes[b]	OHS[c]
Age/longevity	18 years	4 years	26 years	38 years	0–3 years	10 years	≥mid-adulthood
Premature birth	−	+	−	+	+	−	−
Low birth weight	−	−	−	−	+	−	−
Neonatal jaundice	−	+	+	−	+	−	−
Neonatal temperature instability	−	+	−	−	+	−	−
Decreased facial expression	−	+	+	+	+	−	−
Prominent forehead	+	+	+	+	+	−	+
Long face	+	−	+	+	−	−	+
Full cheeks	+	+	+	+	+	+	−
Highly-arched palate	+	+	+	+	+	+	+
Downslanting palpebral fissures	+	+	+	+	−	−	+
Hypopigmented skin	+	+	+	+	+	+	−
Cutis laxa	++++	++	++	+++	++	++	++++
Pili torti	+	+	+	+	+	+	+
Poor motor development	+++	++++	+++	+++	++++	++	−
Poor cognitive development	++	++++	+++	+++	++++	+	+/−
Dysarthria	+++	NA	+++	+++	NA	++	−
Ataxia	−	−	−	−	−	+++	−
Seizure onset	3 years	−	4 years	4 years	<1 year	−	−
Chronic diarrhea	+	−	+	+	−	−	−
Inguinal hernia	+	+	−	+	+	−	+
Bladder diverticula	+	+	+	+	+	−	+
Pectus excavatum	+	+	+	+	+	−	+

*+, finding present with increasing severity from +–+++; −, finding not present; NA, not applicable.
[a]Based on recent review [Kaler, 1994].
[b]Based on most recent clinical description [Danks, 1993].
[c]Based on compiled data [Tsukahara et al., 1994].

The clinical spectrum of Menkes disease encompasses several distinct variants. Individuals with the mild variant are developmentally delayed, with prominent cerebellar ataxia, dysarthria, and pili torti, but without seizures or death in childhood (Table I). Cerebral arteries are elongated, tortuous, and dilated [Procopis et al., 1981; Danks, 1972]. Other children with features-typical-of classical Menkes disease have been described, but with survival beyond early childhood [Gerdes et al., 1988].

Occipital horn syndrome (OHS), previously known as type IX Ehlers-Danlos syndrome or X-linked cutis laxa, represents another confirmed variant [Lazoff et al., 1975; Sartoris et al., 1984; OMIM, 1995]. OHS, an X-linked recessive connective-tissue disorder, derives its name from occipital exostoses (occipital horns) resulting from calcification of the trapezius and sternocleidomastoid muscles at their attachment to the occipital bone. Additional clinical signs are listed in Table I. Autonomic dysfunction with syncope or diarrhea suggestive of deficient activity of DBH may occur. Radiographic abnormalities include osteoporosis, occipital and femoral exostoses, carpal coalescence, coxa valga, deformation of radii, ulnae, tibiae, and fibulae, and short clavicles with hammer-shaped distal ends [Tsukahara et al., 1994].

The identification of the gene responsible for Menkes disease has permitted the demonstration of allelism between the classic phenotype and suspected variants. Levinson et al. [1993] found reduced expression of the Menkes gene in 2 patients with OHS, and splice-site mutations at the Menkes locus in several individuals with OHS have been reported [Kaler et al., 1994; Das et al., 1995]. We studied 4 related males with manifestations of classical and mild Menkes disease and OHS, and we detected a splice-site mutation of the Menkes gene in these 4 individuals [Kaler et al., 1994]. We now detail the natural history and physical and radiographic findings of these 4 patients with a novel allelic variant of classical Menkes syndrome. Portions of this report were previously presented in abstract form [Proud et al., 1993].

METHODS

Medical records were reviewed and a history was obtained from the relatives in the pedigree depicted-in (Fig. 1). Each affected male was evaluated, pertinent physical findings were recorded, and a neurologic examination was performed. In addition, hair samples were examined microscopically and radiographic images were reviewed. Serum copper and ceruloplasmin and plasma catecholamine profiles were reported pre-

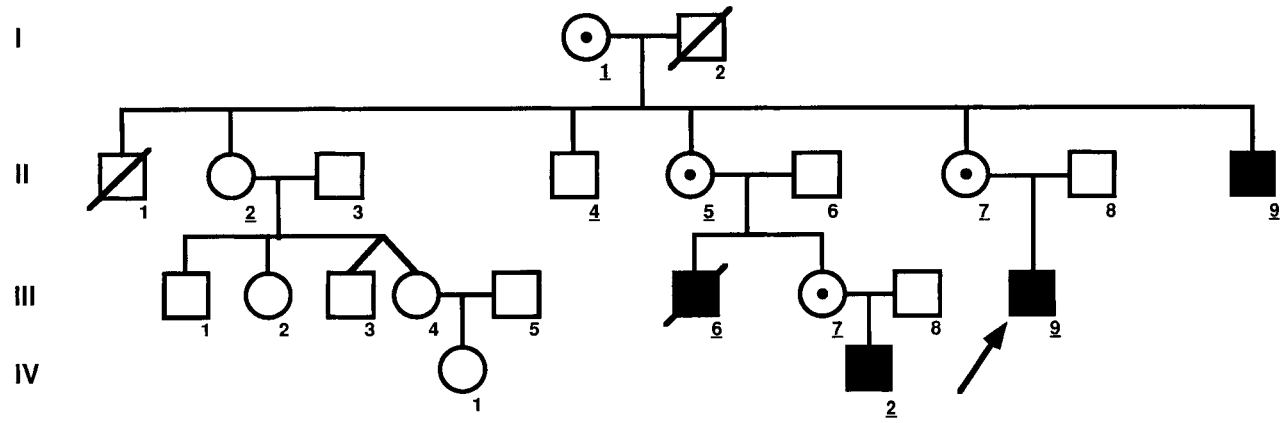

Fig. 1. Family pedigree. ■, affected male; ⊙, carrier female; ↗, propositus; underlined numbers, clinical examination and mutation analysis performed.

viously [Kaler et al., 1994]. A review of family pictures was conducted for each individual, to document evolution of the phenotype.

CLINICAL REPORTS

Patient 1, the propositus (Fig. 1, III-9), is the 18-year-old son of nonhomogeneous parents. He was delivered at term weighing 2.6 kg (5–10th centile). Length was 48 cm (10th centile). Vomiting and diarrhea began within the first week of life. Inguinal hernia repair was performed at 2 months. At 6 months, his weight was 3.9 kg (<5th centile), and pyloromyotomy was performed for suspected pyloric stenosis. His vomiting improved, but diarrhea continued until of age 13 years. Temperature instability was noted during infancy and childhood, with heat intolerance and extreme temperature elevations during the summer. Multiple bladder diverticula resulted in urinary obstruction and recurrent bladder rupture, requiring a suprapubic drain at age 15 months. Vesicoureteral reflux and recurrent urinary tract infections prompted the removal of the right kidney at age 12 years. The bladder was removed at 13 years. Redundant, loose, translucent skin was noted in infancy and worsened with age. Aneurysmal dilatations of both external jugular veins were removed at 13 and 15 months, and multiple joint dislocations occurred throughout childhood and adolescence.

Early visual fixation and tracking were normal. Intermittent ptosis was noted during childhood, and at age 11 years he underwent blepharoplasty. Generalized epilepsy appeared at 3 years and responded readily to antiepileptic agents. He remained seizure-free until age 14 years, when he began to have episodes of altered consciousness with lip-smacking and eye deviation. These were shown to be secondary to profound hypoglycemia and resolved with continuous nasogastric feedings. A spontaneous intracerebral hemorrhage occurred at age 15 years.

His early development was delayed. He sat alone at age 1 year, and walked assisted at 9 years, but never achieved independent ambulation. His voice was dysarthric and speech acquisition was delayed, but at age 15 years he had a large vocabulary and spoke in sentences appropriate for his age. He was able to read and write at a second grade level and perform division. Since the intracerebral hemorrhage, he has been nonverbal but is able to laugh, interact with eye gaze, and smile responsively.

Physical anomalies during infancy included cutis laxa, hypopigmentation of the skin and hair, high-arched palate, prominent ears and forehead, downslanting palpebral fissures, full cheeks, mild hypotonia, and muscle weakness (Fig. 2a). Tooth eruption was not delayed, but dental malocclusion occurred. During childhood his hair became darkly pigmented, but his skin remained hypopigmented (Fig. 2b). At age 18 years, weight was 36 kg (50th centile for 11.5 years old), height was 137 cm (50th centile for 9.5 years old), and head circumference (OFC) was 56 cm (75th centile for age). He was found to have lax and hypopigmented skin, with follicular hyperkeratosis, and coarse and darkly pigmented hair and eyebrows, scoliosis, pectus excavatum, and dislocation and contracture of elbows and hips. Sexual development was Tanner stage 5. The face was long with prominent forehead and large ears. Dental malocclusion with a broad alveolar ridge, high-arched palate, and downslanting palpebral fissures were present. Neurological examination documented eye deviation to the right, no voluntary limb movements, and spastic quadriparesis. Occipital exostoses were palpable. Microscopic examination of the hair showed pili torti.

Patient 2 (Fig. 1, IV-2) is the 4-year-old cousin of patient 1. His premature delivery at 32 weeks of gestation (weight, 1.56 kg, 40th centile; and length, 38 cm, 10th centile) was precipitated by a maternal accident. Neonatally he had hyperbilirubinemia, recurrent apnea and bradycardia, prolonged temperature instability, and left radial head dislocation. Bilateral inguinal hernia and hydrocele repair was performed at of age 2 months. Tooth eruption was delayed. Neither seizures nor chronic vomiting and diarrhea have occurred. He was also heat-intolerant.

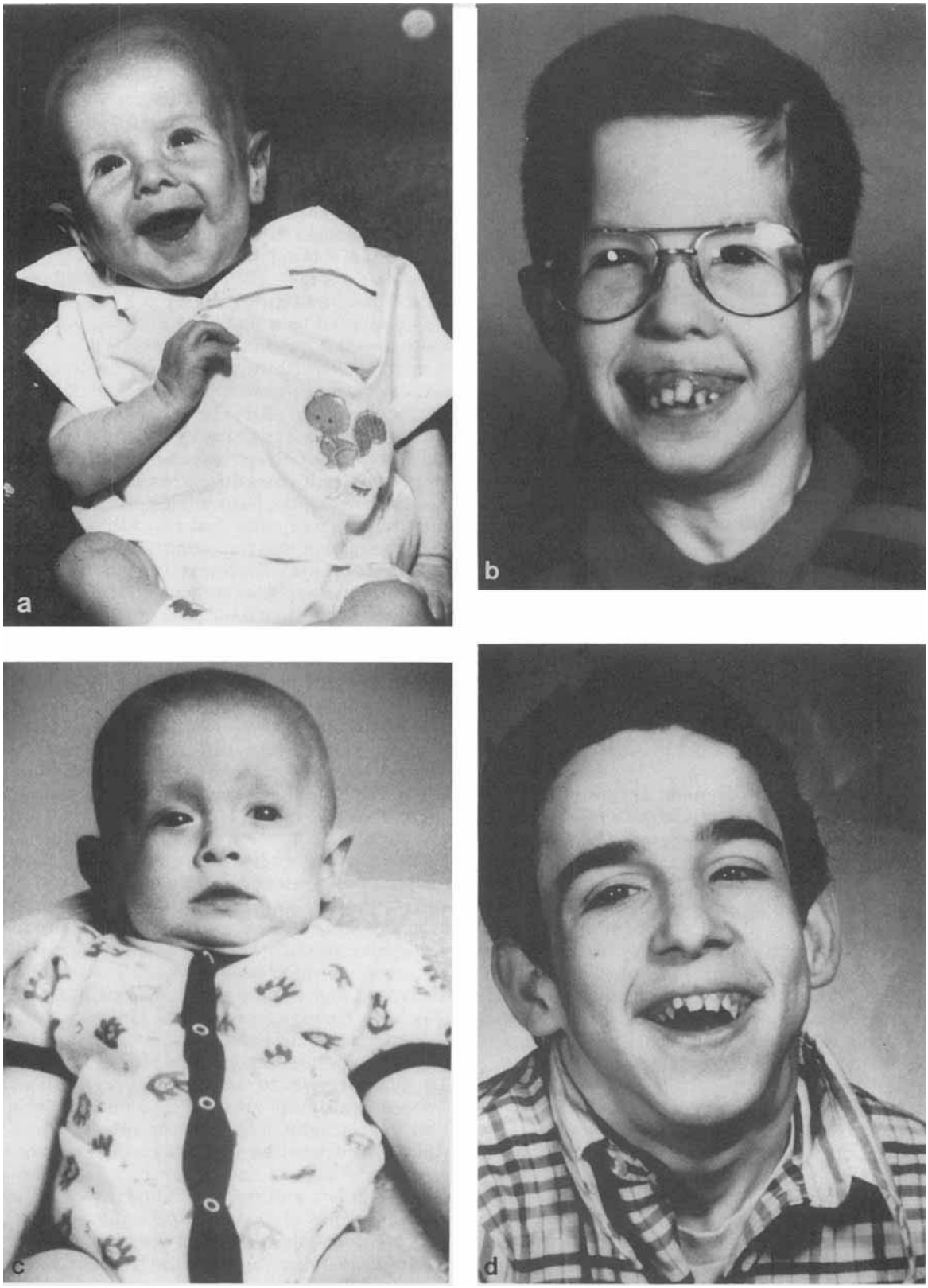

Fig. 2. **a**: Propositus (patient 1), age 5 months. **b**: Propositus (patient 1), age 13 years. **c**: Patient 2, age 11 months. **d**: Patient 3, age 14 years. **e**: Patient 4, age 35 years.

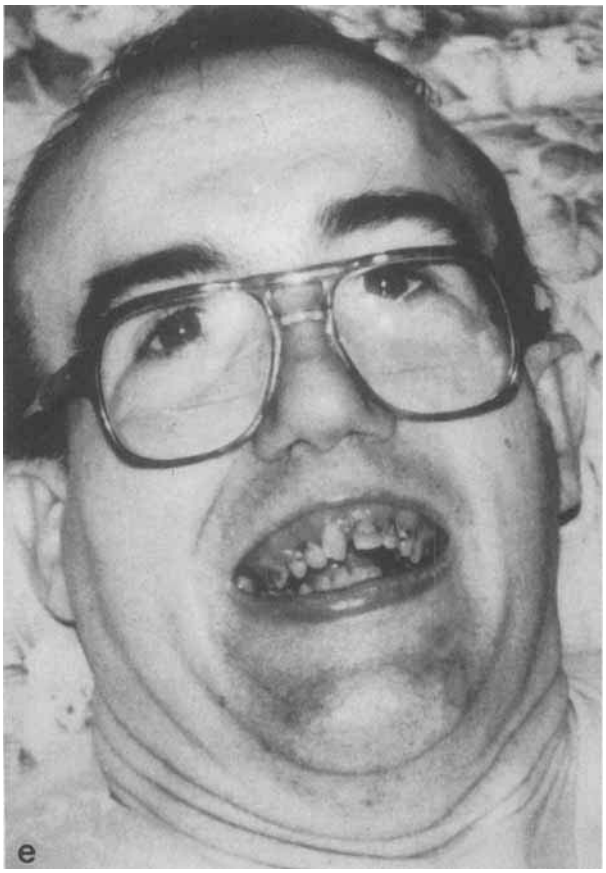

Fig. 2. *Continued.*

His development was consistently abnormal and never comparable to that of patient 1. Presently at age 4 years, he has no words, is only able to roll from back to front, and has very poor head control. He is unable to sit alone, but can reach for objects. His weight is 9.3 kg (50th centile for 9 months), length 83 cm (50th centile for 18 months), and OFC 49 cm (20th centile for 4 years). Abnormal physical findings are similar to those of patient 1. However, as compared to patient 1, his facial expression was decreased (Fig. 2c). Neurologic examination was remarkable for hypotonia, hyperreflexia without clonus, and muscle weakness. Occipital exostoses were not palpable. Microscopic examination of hair showed pili torti.

Patient 3 (Fig. 1, III-6) was the 26-year-old cousin of the propositus. He was born at term weighing 3.5 kg (50th centile). Bilateral cephalohematomas were present, and he developed jaundice. Pyloromyotomy for suspected pyloric stenosis was performed at age 6 weeks. Chronic diarrhea began at age 3 years, and epilepsy was diagnosed at age 4 years.

Tooth eruption was not delayed, but malocclusion occurred (Fig. 2d). Bladder diverticula were present and urinary tract infections frequent. The severity of his developmental delay was intermediate between that of patients 1 and patient 2. Speech was delayed in acquisition, was dysarthric, and consisted of many single words. Comprehension was more better. Death occurred suddenly at age 26 years. An intracranial hemorrhage was suspected, but none was noted at autopsy, and no other cause of death was found.

Physical findings in infancy were similar to those of patient 2, but his hair was darkly pigmented. At 26 years, weight was 51 kg (50th centile for 14 years) and height was 152 cm (50th centile for 12.5 years). OFC was 58 cm (98th centile). Physical traits were similar to those of patient 1. Sexual development was at Tanner stage 5. Spasticity and hyperreflexia were present. Occipital exostoses were palpable. Microscopic examination of hair showed pili torti.

Patient 4 (Fig. 1, II-9) is the 38-year-old uncle of patient 1. His premature delivery at 34 weeks of gestation was prompted by a maternal fall. Weight was 2.24 kg (60th centile). Inguinal hernia repair was performed at 3 months. Failure to thrive with recurrent vomiting and diarrhea was present in infancy, with diarrhea persisting for many years. Dental eruption was delayed. Generalized epilepsy, readily controlled with anticonvulsants, began at age 4 years. Vesicostomy was performed at age 9 years due to obstruction from multiple bladder diverticula. Heat intolerance, especially during the summer, resembled that noted in his nephews. Motor development was comparable to that of patient 1. At age 38 years, his speech was dysarthric and limited to simple sentences. Comprehension was better. He was able to write his name but was unable to read.

Abnormal physical characteristics in infancy were similar to those of patients 1, 2 and 3. At age 38 years, his weight was 71 kg, height 148 cm (50th centile for 11.5 years) and OFC 57 cm (75th centile). Physical abnormalities were similar to those of patient 1 and 3 (Fig. 2e). Muscle tone and strength were normal, and reflexes were hyperactive. Occipital exostoses were palpable. Pili torti of hair was present microscopically.

Radiographic Findings

Radiographic studies in the propositus demonstrated occipital exostoses and anterior wedging of the cervical vertebrae (Fig. 3a, b). The clavicles were short, with hammer-shaped distal ends (Fig. 4). Coxa valga with acetabular dysplasia and dislocation of the right femur were demonstrated at age 5 years. The radial head was dislocated and the ulna was deformed at age 8 years (Fig. 5). Enlargement of the frontal sinuses and pneumatization of the sphenoid wing were evident on cranial computed tomography. MRI of the brain at age 14 years (prior to the intracerebral hemorrhage) showed multifocal areas of encephalomalacia. Cerebral angiography, following the intracerebral hemorrhage, demonstrated severe vascular tortuosity with occlusion of small branches of the middle cerebral arteries, the left anterior cerebral artery, and medium-sized branches of the right posterior cerebral artery. Collateral vessels resembled the "puff of smoke" pattern seen in Moya Moya disease (Fig. 6).

In patient 2, occipital horns were not demonstrated by skull films at age 1 year, but were clearly present on repeat studies at age 4. Wormian bones were prominent on both occasions. The clavicles showed mild hammer-shaped deformities, and hip films demonstrated

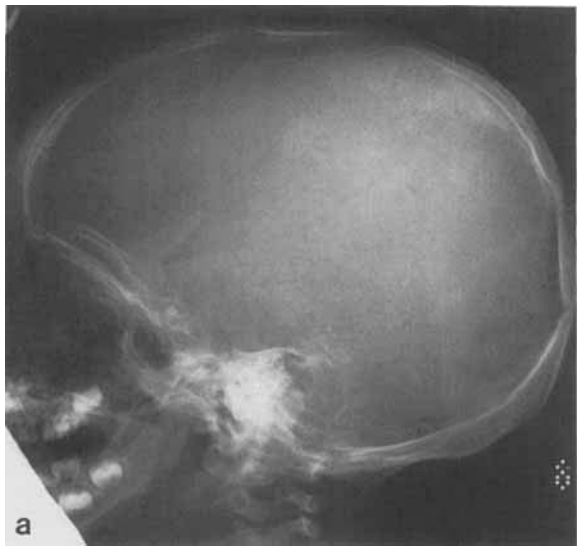

Fig. 3. **a**: Propositus (patient 1), age 3 years. Radiograph demonstrates small occipital exostoses and Wormian bones posteriorly. **b**: Propositus (patient 1), age 15 years. Radiograph demonstrates enlargement of occipital exostoses and anterior wedging of cervical vertebrae.

marked coxa valga at age 4. Bladder diverticula were present at age 2 and by age 4 had progressed dramatically (Fig. 7). Cranial MRI at age 2 years demonstrated normal brain morphology and caudal displacement of the torcula, without evident redundancy of intracranial vasculature. Repeat cranial MRI and MRA imaging at age 4 years demonstrated the additional finding of marked vessel ectasia.

Radiographic abnormalities in patient 3 included occipital horns, loss of mandibular angle, osteophyte formation of vertebrae, and heavily calcified thyroid and arytenoid cartilages (Fig. 8). Radial head dislocation and deformity of the radius and ulna were present, and the clavicles were short with hammer-shaped distal ends. Other radiographic abnormalities consisted of short fourth metacarpal, mild coxa valga, and tibial growth arrest.

DISCUSSION

The clinical and radiographic findings in the 4 affected males from this family comprise a distinctive syndrome which overlaps the classical, mild, and occipital horn variants of Menkes disease. The major aspects of this novel phenotype are moderate-to-severe psychomotor retardation, childhood-onset seizures (at age 3–4 years), dysarthric speech, pili torti, pronounced

Fig. 4. Propositus (patient 1), age 15 years. Radiograph demonstrates shortening and marked distal deformity of clavicle.

Fig. 5. Propositus (patient 1), age 8 years. Radiograph demonstrates radial head dislocation and deformity of ulna.

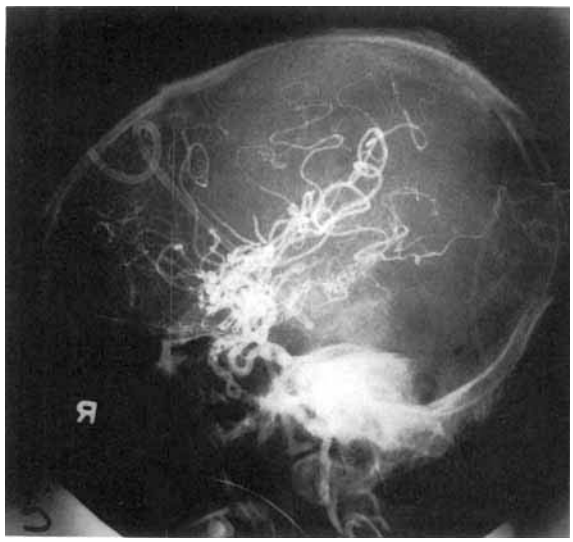

Fig. 6. Propositus (patient 1), age 15 years. Cerebral angiography demonstrates multiple branch occlusions and extensive collateralization with Moya-Moya appearance.

skin laxity, pectus excavatum, deformities elbow dislocations, bladder diverticula, chronic diarrhea, occipital exostoses, and tortuous vessels. Each of these anomalies has been described in one or more of the three recognized Menkes disease variants (Table I), but the specific constellation of abnormalities found in this family does not correspond precisely to any of those variants. In particular, classical Menkes disease would not ordinarily be considered a diagnostic possibility in these relatives due to their longevity, later onset of seizures, and milder neurodevelopmental impairment. Also, classical Menkes patients typically demonstrate asymmetric growth retardation (preservation of height with deceleration of weight and head growth). Conversely, our patients are short in stature and vary in weight,

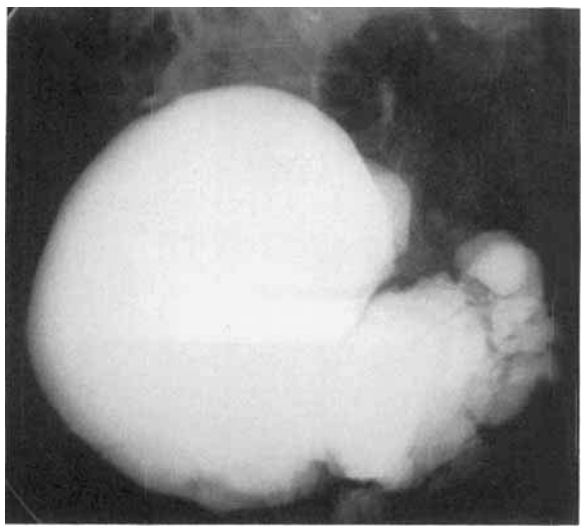

Fig. 7. Patient 2, age 2 years. Voiding cystourogram demonstrates multiple diverticula.

Fig. 8. Patient 3. Radiograph at age 26 years demonstrates occipital exostoses, osteophyte formation, loss of mandibular angle, and calcification of thyroid cartilage.

but, importantly, all have normal head circumferences for age (range of 20–98th centile). In addition, cerebral vascular tortuosity was described in Menkes variants, but the Moya-Moya pattern seen by cerebral angiography in patient 1 was not been reported previously. These males have physical findings and a clinical course which is quite similar to that in a 34-year-old Japanese man described as having Ehlers-Danlos syndrome type IX with severe myopathy and psychomotor retardation [Wakai et al., 1993]. We suggest that this patient manifests the same syndrome/Menkes disease variant as our family, based on his longevity and reported clinical and biochemical abnormalities.

Major deletions in the Menkes gene are detected by Southern blot analysis in 15–20% of individuals with classical Menkes disease [Chelly et al., 1993; Vulpe et al., 1993]. Additionally, splice-site mutations, nonsense mutations, missense mutations, duplications, and small deletions that predict partially deleted or truncated gene product have also been observed [Das et al., 1994; Kaler et al., 1995]. In contrast, the presence of some normal Menkes gene product in the affected males of this family, as predicted by their specific splice-site mutation which allows for up to 20% of normal Menkes gene splicing, may facilitate the availability of copper to certain cuproenzymes and enhanced copper delivery to the brain early in life, accounting for their relatively less severe phenotype compared to clas-

sical Menkes disease. We note that head circumference, a reflection of brain growth, was normal in our patients, in contrast to that in classical Menkes disease, in which acquired microcephaly is typical [Kaler, 1994]. Copper is known to be necessary for normal mammalian brain growth and development [Bennetts and Chapman, 1937], although the precise role and mechanism(s) of action are not clear. It is tempting to speculate that within the spectrum of Menkes disease allelic variants, a relationship between the quantity of functional Menkes copper ATPase and clinical outcome may exist. Further, the variable disease expression within this family may be related, at least in part, to tissue-specific differences in the amount of normal gene product.

Discovery of the gene responsible for classical Menkes disease has permitted molecular analysis of families with potentially related phenotypes including this family, which at first glance did not appear to have a problem related to copper transport. Identification in this family of the molecular defect [Kaler et al., 1994] allowed us to reassure family relatives who are not carriers, and could enable prenatal diagnosis for obligate carriers (Fig. 1) on molecular grounds.

In summary, we propose a new clinical variant of Menkes disease, represented by the 4 affected males described here and 1 previously reported from Japan [Wakai et al., 1993]. Males with developmental delay or mental retardation and connective tissue abnormalities should be evaluated for biochemical evidence of defective copper transport by determination of serum copper and ceruloplasmin and/or plasma catecholamine levels.

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